



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Darrell R. Anderson et al.

Group Art Unit: 1644

Application No. 08/746,361

Examiner: P. Gambel

Filed: November 8, 1996

Title: IDENTIFICATION OF UNIQUE BINDING INTERACTIONS BETWEEN CERTAIN ANTIBODIES AND THE HUMAN B7.1 AND B7.2 Co-STIMULATORY ANTIGENS

* * * * *

DECLARATION OF DARRELL R. ANDERSON, Ph.D.

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, declare and state as follows:

1. That I am the same Darrell R. Anderson who is an inventor of the above-identified application.
2. That I understand that the Examiner has maintained his position that it allegedly would have been obvious to have derived monoclonal antibodies that specifically inhibit the interaction of B7.1 antigens with CD28, but which do not inhibit the interaction of B7.1 antigens with CTLA-4 as of the time this application was filed. The Examiner relies especially on a patent assigned to Chiron, which names deBoer et al. as the inventors, U.S. Patent 5,757,034, and a patent assigned to Bristol Meyer Squibb, by Linsley et al., U.S. Patent 5,770,197. The Examiner states particularly in the most recent Office Action that the subject antibodies are unpatentable because Linsley et al. purportedly suggests the use of anti-B7.1 antibodies to inhibit interactions of CD28-positive cells "or" CTLA-4-positive cells with B7 cells and that this provides a "reasonable expectation of success" (the generation of antibodies that selectively inhibit interaction of B7.1 with CD28 but which do not inhibit interaction of B7.1 with CTLA-4.) I respectfully disagree.

3. I have carefully reviewed the Linsley et al. and DeBoer patents, including the passages at Col. 15, para. 7 (lines 60-65) relied upon by the Examiner. In my estimation as an expert in the field of co-stimulatory molecules, recombinant antibodies and their potential use as therapeutic, at best these references teach that B7.1 was known to interact with CTLA-4 and CD28 and that anti-B7.1 antibodies potentially could be obtained which inhibit such interactions. However, these references fail to provide a reasonable expectation that antibodies could be obtained that *selectively* inhibit the interaction of B7.1 with CD28, but which do not inhibit the interaction of B7.1 with CTLA-4. Particularly, there is no teaching that a separate and distinct epitope on human B7.1 exists which is instrumental in CD28 interaction, to which an antibody could be generated against and that such antibody will not inhibit the interaction of B7.1 with CTLA-4.

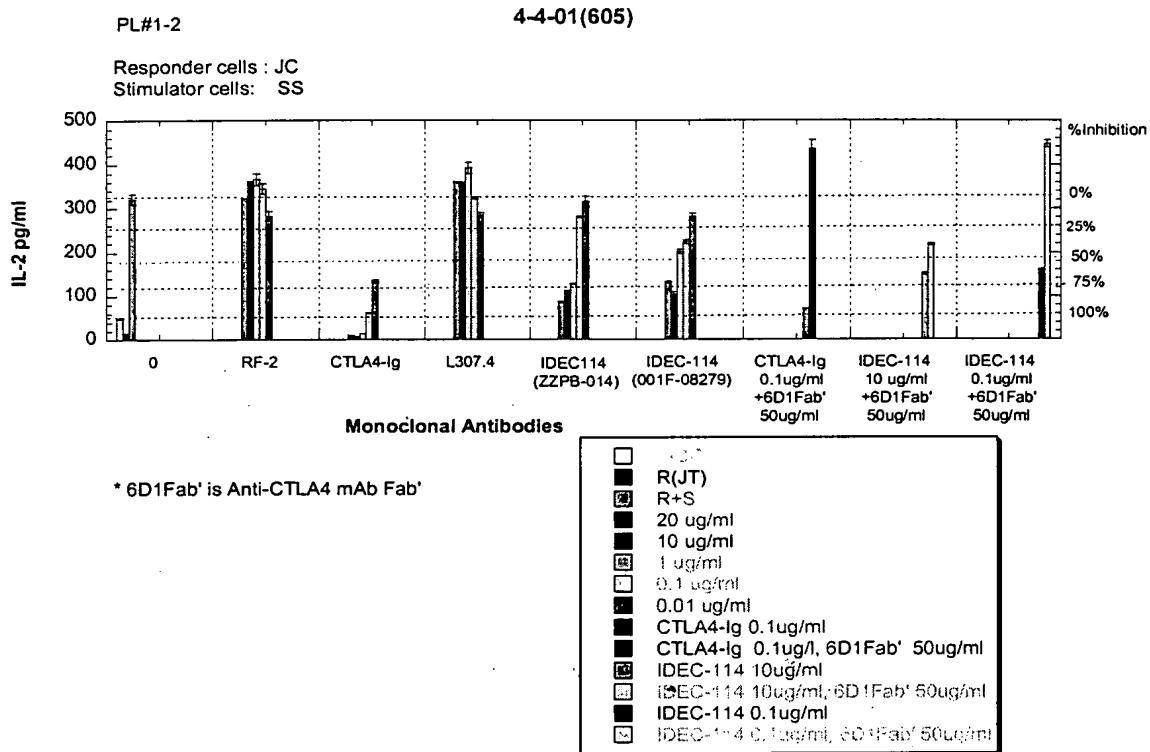
4. In my opinion, the non-trivial and unexpected nature of the outcome is strongly supported by the fact that even to date, the antibodies disclosed by us in this application are the only known anti-B7.1 antibodies reported that exhibit this unique and desirable binding characteristic.

5. It is further my opinion, that the unexpected nature of the outcome is supported by the manner that subject antibodies were obtained. Particularly, the subject antibodies were generated in cynomolgus monkeys. With respect thereto, it should be emphasized that cynomolgus monkey and human antigens are typically highly evolutionarily conserved. For example, the variable regions of antibody sequences between these species exhibit on average \leq from between 85-98% sequence identity. Thus, B7.1 antigens in humans and cynomologus monkeys would similarly be expected to be highly conserved. Given this expectation, it would have been predicted that the human B7.1 antigen will present very few epitopes that would be recognized as foreign in a cynomolgus monkey. This renders

the outcome even more unexpected, i.e., that a cynomolgus monkey would produce antibodies against an epitope that was never even known to exist even when B7.1 was utilized as an immunogen in species much more evolutionarily removed from humans (rodents). Particularly, as established by my earlier declaration, all prior art of which I am aware relating to B7.1 antibodies (which have been produced in rodents) cross-react with CTLA-4. This makes the inventive result even more unexpected.

6. I further believe that the subject antibodies constitute a significant advance in the field because they exhibit distinct functional characteristics vis-à-vis anti-B7.1 antibodies that interact with CTLA-4. This difference is substantiated by the functional behavior of an antibody according to the invention (referred to as 16C10 in the application and more recently referred to by the subject Assignee as IDEC-114) to another anti-B7.1 antibody reported by Nickoloff et al. that blocks B7.1 interaction with CTLA-4. These anti-B7.1 antibodies as well as a positive control (CTLA-4-Ig fusion protein) and a negative control (irrelevant human IgG antibody to RSV fusion protein, RF2) were compared in a number of mixed lymphocyte reactions (MLRs). The results of a representative MLR experiment comparing these immune molecules are set forth on the following page:

The Effect of IDEC-114 on IL-2 Production of Human PBMC MLR Assay



It can be seen therefrom that CTLA-4Ig, blocked both B7-1 and B7-2 interactions with CD28 (positive control). It can also be seen that while IDEC-114 effectively blocked IL-2 production when B7.2 antigens were present, the other anti-B7.1 antibody (L307.4) had no such inhibitory effect. Similar results were obtained with other MLRs run by us under the same conditions. These results clearly show that antibodies according to the invention exhibit differences functional properties and mechanisms relative to previous other anti-B7.1 antibodies. In my opinion, these differences are unexpected and are most probably a consequence of the unique binding interaction of the subject anti-B7.1 antibodies.

7. It further has recently been shown that anti-B7.1 antibodies according to the invention exhibit in vivo characteristics that support their clinical use for treatment of T cell mediated disorders such as psoriasis. Evidence relating thereto is contained in a draft

manuscript attached to this Declaration as Exhibit A. This manuscript contains preliminary clinical trials wherein IDEC-114 was administered to 24 psoriasis patients (open-label, single dose, dose-escalatory study in patients with moderate to severe chronic plaque psoriasis.) Based on the observed "Psoriasis Area and Severity Index", "Physician's Global Assessment", and "Psoriasis Severity Scale", which comprise an accepted means for evaluating the prognosis of psoriasis patients, IDEC-114 appears to be safe, well-tolerated and exhibits promising clinical activity (average plaque thickness and plaque CD3+/CD8+ T cell numbers decreased in patients administered 10 mg/kg of IDEC-114). (See results in Exhibit). These results support a conclusion that anti-B7.1 antibodies according to the invention will provide an effective therapy for treatment of psoriasis as well as other T cell mediated diseases.

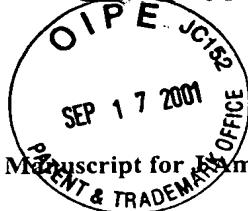
8. I also understand that the Examiner has cited our earlier patent as prior art to the claimed invention. With respect thereto, it should be noted that the additional inventor, William Shestowsky, was a named inventor on the earlier patent because of his contribution to the particular antibody sequences that were claimed therein. However, he is properly not a named inventor with respect to the subject claims, none of which are directed to these specific antibody sequences. Thus, the disclosure in our earlier patent does not constitute work by another within the context of the present invention.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the

United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____

Darrell R. Anderson, Ph.D.



DRAFT 114-01 Manuscript for JXmer Acad Dermatology

Single-Dose Treatment of Moderate to Severe Psoriasis With a PRIMATIZED® Anti-CD80 Monoclonal Antibody

DRAFT

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References; 0 Tables; 2 Figures

ABSTRACT

Pathologic T-cell activation is implicated in psoriasis progression. CD80, a costimulatory molecule involved in T-cell activation, likely plays a key role. IDEC-114, a PRIMATIZED® anti-CD80 antibody, was evaluated for safety, pharmacokinetics, and preliminary clinical activity in this open-label, single-dose, dose-escalating study in patients with moderate to severe chronic plaque psoriasis. Twenty-four patients received IDEC-114 (0.05 mg/kg, 0.25 mg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, or 15 mg/kg). Adverse events were primarily mild, transient, constitutional symptoms; the most common were Grade 1/2 asthenia (29% of patients), chills (25%), and headache (21%). IDEC-114 serum half-life was approximately 13 days. Psoriasis Area and Severity Index, Physician's Global Psoriasis Assessment, and Psoriasis Severity Scale scores improved in the highest dose groups. Average plaque thickness and plaque CD3+/CD8+ T-cell counts decreased in 10 mg/kg patients. IDEC-114 is safe, well tolerated, and has promising clinical activity in psoriasis.

Word count: 142 (maximum, 150)

INTRODUCTION

Psoriasis, an inflammatory skin disorder, is characterized by abnormal keratinocyte differentiation and proliferation mediated by activated T cells[Greaves, 1995 #665; Krueger, 1995 #670; Gottlieb, 1995 #664; REF: NEW Valdimarsson H, 1986^a #]. T-cell activation requires two signals from antigen-presenting cells (APCs)[REF: NEW Bretscher, 1970^b #; REF: NEW Bretscher, 1999^c #; REF: NEW Chambers, 1999^d #]. The primary signal is mediated by T-cell receptor interaction with a specific antigen bound to MHC; the second, antigen-independent signal is mediated by a variety of costimulatory molecules.

CD80 (B7-1) and CD86 (B7-2), members of the growing B7 costimulatory molecule family[Dong, 1999 #1376; REF: NEW Wang, 2000^e #; REF: NEW Chapoval, 2001^f #], provide the second signal to activate T cells via independent, low-affinity binding with their receptor, CD28, which is expressed constitutively on unstimulated T cells. CD28 is normally involved in the regulation of cell-cycle progression, cell survival, and cytokine production. When CD28 is absent or blocked in a variety of murine inflammatory disease models, disease severity is reduced considerably[REF: NEW Tada^g, 1999 #; REF: NEW Girvin^h, 2000 #; REF: NEW Oliveira-dos-Santosⁱ, 1999 #; REF: NEW Mathur^j, 1999 #].

T-cell activation leads to the expression of a second member of the CD28 family, CD152 (cytotoxic T lymphocyte-associated antigen-4; CTLA-4), a high-affinity CD80 and CD86

^a Valdimarsson H, 1986, Psoriasis: A disease of abnormal keratinocytic proliferation induced by T-lymphocytes. *Immunol Today* 7:256

^b Bretscher, 1970, A theory of self-nonself discrimination. *Science* 169:1042-1049

^c Bretscher, 1999, A two-step, two-signal model for the primary activation of precursor helper T cells. *Proc Natl Acad Sci USA* 96, 185-190

^d Chambers, 1999, Costimulatory regulation of T cell function. *Curr Opin Cell Biol* 11, 203-210

^e Wang, 2000, Costimulation of T cells by B7-H2, a B7-like molecule that binds ICOS. *Blood* Oct 15;96(8):2808-2813

^f Chapoval, 2001; B7-H3: A costimulatory molecule for T cell activation and IFN-gamma production. *Nature Immunology* Mar;2(3):269-274

^g Tada Y, 1999, Role of the costimulatory molecule CD28 in the development of lupus in MRL/lpr mice. *J Immunol* 163:3152-3159.

^h Girvin AM, 2000, A critical role for B7/CD28 costimulation in experimental autoimmune encephalomyelitis: A comparative study using costimulatory molecule-deficient mice and monoclonal antibody blockade. *J Immunol* 164:136-143.

ⁱ Oliveira-dos-Santos A, 1999, CD28 costimulation is crucial for the development of spontaneous autoimmune encephalomyelitis. *J Immunology* 162:4490-4495.

^j Mathur M, 1999, CD28 interactions with either CD80 or CD86 are sufficient to induce allergic airway inflammation in mice. *Am J Respir Cell Mol Biol* 21:498-509.

counter-receptor[REF: NEW Brunet, 1987^k #]. CD80 or CD86 binding to CD152 initiates an intracellular signaling cascade that downregulates T-cell activation and thus counteracts CD28-mediated costimulation. CD152 deficiency results in a profound lymphoproliferative disorder with early lethality, confirming the role of CD152 as a negative regulator of T-cell activation[REF: NEW Waterhouse, 1995^l #].

Although the costimulatory functions of CD80 and CD86 are similar, their unique role in T-cell activation remains unclear. Both CD80 and CD86 are upregulated on APCs following T-cell activation, as well as on certain activated T cells in psoriatic lesions[Nickoloff, 1994 #678; REF: NEW Ferenczi, 2000^m #]; however, their temporal expression, density, and kinetics are differentially regulated. CD86 is expressed constitutively and is upregulated quickly, and is therefore expected to play a more important role in the activation of immune responses, whereas CD80 is upregulated more slowly and may be more important in sustaining or regulating the response. CD80 binds more strongly to CD152[Linsley, 1994 #674]; its biologically relevant role may be to terminate activation via CD152. Because persistent T-cell activation is implicated in the pathophysiology of psoriasis, the costimulatory pathway, and CD80 in particular, provides a key target for therapies directed against this chronic, inflammatory skin disorder.

CTLA4-immunoglobulin (CTLA4Ig; Bristol-Myers Squibb 188667), a soluble fusion protein that blocks CD80 and CD86 interactions with both CD28 and CD152, has demonstrated a clinical effect in psoriasis and an effect on the T-cell-dependent antibody response to novel antigens such as keyhole limpet hemocyanin and Φ X174[REF: NEW Abrams, 2000ⁿ #; Abrams, 1999 #1110]. Because CTLA4Ig binds both CD80 and CD86, in addition to preventing CD28-mediated T-cell activation, CTLA4Ig likely interferes with CD152-mediated T-cell downregulation.

^k Brunet JF, 1987, A new member of the immunoglobulin superfamily CTLA-4. *Nature* 328, 267-270

^l Waterhouse P, 1995, Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. *Science* 270(5238):985-988.

^m Ferenczi, 2000, CD69, HLA-DR and the IL-2R identify persistently activated T cells in psoriasis vulgaris lesional skin: blood and skin comparisons by flow cytometry. *J Autoimmun* Feb;14(1):63-78

ⁿ Abrams, 2000, Blockade of T lymphocyte costimulation with Cytotoxic T Lymphocyte-Associated Antigen 4-Immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J Exp Med* 192 (5):681-693

IDEc-114, a PRIMATIZED®[Newman, 1992 #677] anti-CD80 (anti-B7-1) monoclonal antibody, has human constant regions and variable primate (cynomolgus macaque) regions. IDEc-114 blocks binding of CD80 with CD28 but not with CD152, and therefore is not expected to interfere with CD152 regulation and function. Consistent with an interference with normal CD28 function, preclinical studies with anti-CD80 antibodies resulted in a delayed progression of autoimmune diseases such as autoimmune diabetes, murine lupus, and chronic, relapsing experimental allergic encephalomyelitis[Gallon, 1997 #661; Herold, 1997 #667; Kuchroo, 1995 #639; Lenschow, 1995 #673; Nakajima, 1995 #676]. IDEc-114 appears to be safe; no adverse reactions were observed in a toxicology study in which primates received up to 30 mg/kg weekly times five and then monthly times five.

Because IDEc-114 targets only CD80 and does not prevent its binding to CD152, its clinical activity in psoriasis may be different than the activity seen with CTLA4Ig. The current study was designed to examine the clinical and immunohistologic effect of CD80 blockade with IDEc-114 in patients with moderate to severe plaque-type psoriasis.

PATIENTS AND METHODS

Eligibility

Eligible patients at least 18 years of age were required to have chronic, stable plaque psoriasis involving $\geq 10\%$ of the body surface area. Patients were to have a baseline Psoriasis Severity Scale[Perkins, 1993 #1216] score of ≥ 6 for at least two plaques located in the trunk, chest, abdomen, and/or proximal extremities; each plaque was to be at least 2 inches square. Patients were required to have failed topical corticosteroids. In addition, patients were to have a CD4+ T-cell count of ≥ 450 cells/ μL within 2 weeks prior to IDEC-114 infusion. No systemic psoriasis therapy or phototherapy/photochemotherapy was allowed within 4 weeks prior to baseline evaluation, and no topical therapy except simple emollients was allowed within 2 weeks. All patients were required to provide written informed consent, and each participating clinical site had to obtain institutional board approval to conduct this study.

Study Design

This open-label, single-dose, dose-escalating clinical study was designed to evaluate the safety, pharmacokinetics, and clinical activity of single infusions of IDEC-114 in patients with moderate to severe chronic plaque psoriasis. Cohorts of three to five patients were to be treated with a single intravenous infusion of IDEC-114 at 0.05 mg/kg, 0.25 mg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, or 15 mg/kg. Two target plaques, each measuring approximately two inches square, were to be followed throughout the study. Follow-up data were to be collected through Study Day 29 for patients in the 0.05 mg/kg and 0.25 mg/kg dose groups, and through Study Day 85 for patients in the 1 mg/kg, 5 mg/kg, 10 mg/kg, and 15 mg/kg dose groups. Treatment with other psoriasis medications was to be prohibited through Study Day 29.

Study Procedures

Clinical activity was assessed by the investigator using the Psoriasis Area and Severity Index (PASI)[Fredriksson, 1978 #746], the Physician's Global Assessment (PGA) [REF: to be determined], and the Psoriasis Severity Scale (PSS). The PASI quantifies the extent of the disease and allows an assessment amount of improvement with treatment when

successive scores are compared. The PGA describes the physician's assessment of the patient's overall response to treatment, and the PSS rates the severity of a psoriatic target lesion. Assessments were performed at baseline (PASI and PSS) and on Study Days 8, 15, and 29 (PASI, PGA, and PSS). The same investigator was to perform all of the assessments.

PASI score calculation required visual assessment of the extent of psoriatic involvement in four main body areas: the head, trunk, upper extremities, and lower extremities corresponding to 10%, 30%, 20%, and 40% of the total body area, respectively. Each area was assigned a numeric value from 0 (no involvement) to 6 (90% to 100% involvement). In addition, each area was assessed for severity of symptoms including scaling, erythema, and induration or plaque elevation. Each symptom was assigned a numeric value from 0 (no symptoms) to 4 (severe symptoms). To obtain the PASI score, the sum of the severity rating for each symptom was multiplied with the numeric value of the areas involved and with the percentage of body area for each of the four main body areas; the resulting four values were added. PASI score units range from 0 (no psoriatic lesions) to 72 (total erythroderma of maximum severity) in 0.1 unit steps.

The PGA rating is based on improvement (percentage clearing) of psoriatic symptoms following treatment as assessed by the clinical investigator. Symptoms were assessed visually and included scaling, erythema, and induration or plaque elevation; each was rated on a scale of 1 to 6, as follows: 1, Clear (100% clear); 2, Excellent (75% - 99% clear); 3, Good (50% - 74% clear); 4, Fair (25% - 49% clear); 5, Poor (0% - 24% clear); and 6, Worse.

The PSS score was used to evaluate the severity of psoriatic symptoms (scaling, erythema, and induration or plaque elevation) for each of the two target plaques. Each symptom was assessed visually for severity and was assigned a numeric score; the values were added for each of the two target plaques to obtain the total PSS score. The total score ranged from 0 to 12, as follows: 0, no symptoms; 3, mild; 6, moderate; 9, severe; and 12, very severe symptoms.

Histopathologic and immunohistochemical evaluations were performed on 6-mm punch skin biopsies of each target plaque at baseline (Day 1) and Day 15. Evaluations included

measurement of average epidermal thickness and counts of both CD3+ and CD8+ cells, and of Ki67, an epidermal cell keratinocyte proliferation marker. In addition, staining was scored as increased or decreased for cells positive for ICAM-1, a cell adhesion molecule upregulated in active psoriatic plaques, and for K16 keratin, a keratinocyte differentiation marker. Biopsy samples were classified as improved if no reduction in ICAM-1 or K16 staining was apparent. Dr. A. Abdulghani performed all evaluations at the University of Medicine and Dentistry of New Jersey. Results of punch skin biopsies were compared with PGA results on Day 15.

Safety evaluations included examination of clinical adverse events, hematology and blood chemistry laboratory results, peripheral blood lymphocyte subpopulations, serum concentrations of IDEC-114, and anti-IDECA-114 antibody. Toxicity was evaluated according to the National Cancer Institute Adult Toxicity Criteria (version 2.0). Peripheral blood lymphocyte subpopulations were monitored using flow cytometry, and serum concentrations of IDEC-114 and anti-IDECA-114 antibodies were measured using validated assays at IDEC Pharmaceuticals.

Pharmacokinetic analysis of IDEC-114 included calculation of the following parameters: the maximum concentration (C_{max}) was the observed value; the area under the curve (AUC) was calculated using the linear/logarithmic trapezoidal method with time extrapolated to infinity; serum half-life, clearance, and volume of distribution were determined using noncompartmental linear regression. Data were to include all samples with detectable IDEC-114 concentrations ($> 0.5 \mu\text{g/mL}$) drawn after Study Day 1 (i.e., 24 hours post-treatment).

RESULTS

Patients

Twenty-four eligible patients were treated at two study sites between October 26, 1998 and June 29, 1999. Patient characteristics included a median age of 43 years (range, 18 to 75 years); 71% male; and 71% Caucasian. Patients' mean baseline scores were 8.2 for PSS (reference range, 0 – 12) and 22.9 for PASI (reference range, 0 – 72). Within 30 days prior to treatment, half received at least one psoriasis therapy that included topical corticosteroids (21%), topical antipsoriatic (17%), or other therapies (12%). Prior

to receiving IDEC-114, patients had discontinued systemic psoriasis treatment for at least 26 days and topical treatment for at least 13 days.

Patients received a single infusion of IDEC-114 in cohorts of either three (patients received 0.05 mg/kg, 0.25 mg/kg, or 1 mg/kg) or five (patients received 5 mg/kg, 10 mg/kg, or 15 mg/kg). All received the scheduled infusion; no patient discontinued treatment or required dose reduction. All had punch skin biopsies of two target plaques on Study Days 1 and 15. All patients were evaluable for safety and all were evaluable for efficacy through Study Day 15. One patient's efficacy evaluation on Day 29 was excluded due to initiation of cyclosporine treatment on Day 16. Nineteen patients completed all follow-up visits.

Safety

Adverse events consisted primarily of mild and transient constitutional symptoms; all related events were Grade 1 or 2. The most common related events were asthenia (29% of patients), chills (25%), headache (21%), dizziness (17%), infection (13%), and fever (13%). Nearly one-third of all related events (29%; 15 of 51) occurred on an infusion day; the most frequent were asthenia (27%) and chills (27%). No relationship was apparent between IDEC-114 dose and either the frequency or severity of adverse events. No Grade 4 or serious adverse events were reported. One patient with chronic bronchitis in the 1 mg/kg IDEC-114 dose group experienced Grade 3 dyspnea on Study Day 43. No hospitalization was required; the patient recovered within four hours and the event was considered unrelated to study medication.

Mean peripheral blood lymphocyte counts (CD3+, CD4+, CD8+, and CD19+) were reduced 30% to 40% in all patients on Study Days 2 and 3; counts recovered by Study Day 15. Five patients experienced six infections (three episodes of respiratory infection; one episode each of bronchitis, influenza, and urinary tract infection). All were Grade 1 or 2; all patients recovered. No cytokine-mediated or infusion-related syndrome was apparent.

One patient in the 0.05 mg/kg IDEC-114 dose group developed a transient anti-IDECK-114 antibody response that was detected on Study Days 15 and 29. The

patient experienced no unusual adverse events and the antibody response was not detectable at study exit.

Pharmacokinetics

The serum half-life of IDEC-114 was approximately 13 days in patients who received single doses of 5 mg/kg to 15 mg/kg. Mean C_{max} was proportional to the IDEC-114 dose administered, and ranged from $0.6 \pm 0.1 \mu\text{g}/\text{mL}$ to $418.8 \pm 79.4 \mu\text{g}/\text{mL}$ in patients who received 0.05 mg/kg and 15 mg/kg, respectively. Similarly, mean AUC was dose proportional and ranged from $1255 \pm 132 \mu\text{g}\cdot\text{hr}/\text{mL}$ to $129,743 \pm 12,114 \mu\text{g}\cdot\text{hr}/\text{mL}$ in patients who received 0.25 mg/kg and 15 mg/kg IDEC-114, respectively. No significant difference was noted in either clearance rate or volume distribution among dose groups. Serum IDEC-114 concentration was below the lower limit of detection ($> 0.5 \mu\text{g}/\text{mL}$) in the majority of samples from patients who received 0.05 mg/kg; therefore, C_{max} was the only pharmacokinetic parameter determined for this dose group.

Response to IDEC-114 Treatment

Mean total PASI score improved by 30% from baseline through Study Day 29 in patients who received a single infusion of 10 mg/kg IDEC-114. Similarly, a 14% improvement was noted through Study Day 29 in patients who received 15 mg/kg. Improvement in mean PASI score was 8%, 11%, and 3% in patients who received 0.05 mg/kg, 0.25 mg/kg, and 1 mg/kg, respectively. No improvement in mean PASI score was noted in patients who received 5 mg/kg. Mean percent improvement from baseline in the PASI score is presented in Figure 1.

Overall PGA ratings improved from baseline to Day 29 in 4 of 5 patients who received 10 mg/kg IDEC-114. Patients' ratings were Excellent (1 patient), Fair (3), and Poor (1) for patients who received 10 mg/kg compared with ratings of Fair (4), Poor (12), or Worse (2) for the remaining patients. Ratings at Day 29 for 15 mg/kg IDEC-114 patients were Fair (2 patients); Poor, and Worse (1 patient each). One patient in the 15 mg/kg dose group received concomitant medication and was excluded from the evaluation.

At Day 15, the PGA ratings at Day 15 were Good (3 patients), Fair (1), and Poor (1) for the 10 mg/kg dose group compared with ratings of Fair (5), Poor (13), and Worse (1) for

the remaining patients. No substantial improvement in PGA rating was noted in patients who received < 10 mg/kg.

Mean total PSS scores improved from baseline to Day 29 in all but the lowest IDEC-114 dose group (0.05 mg/kg; see Figure 2). A 32% improvement was noted through Study Day 29 in patients who received a single 10 mg/kg infusion. Similarly, a 23% improvement was noted through Study Day 29 in patients who received 15 mg/kg. Improvement in mean PSS score was 19%, 5%, and 10% in patients who received 0.25 mg/kg, 1 mg/kg, and 5 mg/kg IDEC-114, respectively. No improvement in mean PSS score was noted in patients who received 0.05 mg/kg.

Mean decreases of 22% and 25% were noted in the average thickness of plaque biopsies at Day 15 in patients with PGA ratings of Good (N = 3) and Fair (N = 6), respectively. Overall, the average thickness of plaque biopsies increased in patients with PGA ratings of Poor (N = 14) or Worse (N = 1); however, decreases were noted in some patients with Poor ratings. Mean percent decreases were noted in counts for CD3+ cells (64%), CD8+ cells (54%), and Ki-67+ cells (36%) in patients with Good PGA ratings; smaller decreases were noted in patients with Fair ratings; and mean percent increases were noted in those with Poor ratings. Results of ICAM-1 and K16 staining were variable. One patient with a Good PGA rating showed improvement in ICAM-1 and K16-staining (i.e., staining remained stable compared with baseline); two patients with a Good rating showed no improvement. Similarly, four of six patients with a Fair rating had improved K16 staining but only three had improved ICAM-1 staining. K16 staining improved in 12 of 14 patients with a Poor rating; ICAM-1 staining improved in only five.

DISCUSSION

A variety of biologic therapies that target one of several immunologic pathways have been tested in psoriasis; each has potentially different actions compared with IDEC-114. For example, both hu-1124, an anti-CD11a monoclonal antibody[REF: NEW Gottlieb, 2000^o #; Gottlieb, 1998 #723], and LFA3/TIP, an anti-CD2 fusion protein[REF: unknown; (*LFA3 is CD58*)], target surface molecules that are widely expressed on a large number of T cells. These molecules have been shown to have clinical activity; however, a variety of adverse events have been noted (such as? ref?). For this reason, evaluation of additional agents is desirable.

The fusion protein, CTLA4Ig, targets both CD80 and CD86 costimulatory molecules and has been shown to have clinical activity[Linsley, 1991 #637]. Since multiple cell types express both CD80 and CD86 in psoriasis lesional skin, interruption of CD80 costimulatory function with IDEC-114 in psoriasis patients provides a unique opportunity to investigate the contribution of CD80 to the immunopathogenesis of this disease.

The adverse event profile was mild following treatment with IDEC-114; no Grade 4 or serious adverse events were reported. No patient discontinued treatment due to adverse events. The most common related events were primarily transient Grade 1 or Grade 2 constitutional symptoms including asthenia, chills, headache, and dizziness. In addition, no relationship was apparent between the dose of IDEC-114 and adverse event severity or frequency. This mild adverse event profile may result from the comparatively restricted expression of CD80, which potentially allows a precise targeting of the antibody to APCs and T cells directly involved in the pathogenesis of psoriasis.

Transient, reversible reductions in mean counts of peripheral blood lymphocytes (CD19+ B cells and CD3+, CD4+, and CD8+ T cells) were observed in all patients but resolved by Day 8. No patient experienced Grade 3 or Grade 4 infection, nor was any patient hospitalized for an infection. Furthermore, no cytokine-mediated or infusion-related syndrome was apparent.

^o Gottlieb, A, 2000, Effects of administration of a single dose of a humanized monoclonal antibody to CD11a on the immunobiology and clinical activity of psoriasis. J Amer Acad Derm March 42(3): pp?

Serum half-life of IDEC-114 was approximately 13 days in patients who received single doses of 5 mg/kg to 15 mg/kg. Mean C_{max} and AUC were dose-proportional, and no significant difference was noted in either clearance rate or volume distribution among dose groups.

Preliminary evidence of clinical activity was demonstrated with single doses of IDEC-114 at 10 mg/kg and 15 mg/kg. Mean total PASI scores improved by 30% and 14% from baseline through Study Day 29 in patients who received a single infusion of 10 mg/kg and 15 mg/kg, respectively. Similarly, the overall PGA ratings improved in patients who received 10 mg/kg compared with ratings for all other patients. Finally, mean total PSS scores improved from baseline to Day 29 in all but the lowest IDEC-114 dose group (0.05 mg/kg). These findings were substantiated with results from plaque biopsies; patients in the 10 mg/kg dose group with Good ratings had mean decreases of 22% in average plaque thickness as well as mean percent decreases in counts for CD3+ cells (64%), CD8+ cells (54%), and Ki-67+ cells (36%). Such reductions in T cells in the skin are consistent with the theoretical mechanism of action of an anti-CD80 monoclonal antibody. These results suggest potential clinical value in treating psoriasis patients with multiple doses of IDEC-114.

The present study provides novel clinical information about the effect of CD80-targeted costimulatory blockade in plaque-type psoriasis. Based on the favorable safety profile and preliminary evidence of clinical activity, monoclonal antibody targeting of CD80 alone provides a theoretically sound and potentially clinically effective route for treating patients with psoriasis as well as other T-cell mediated diseases.

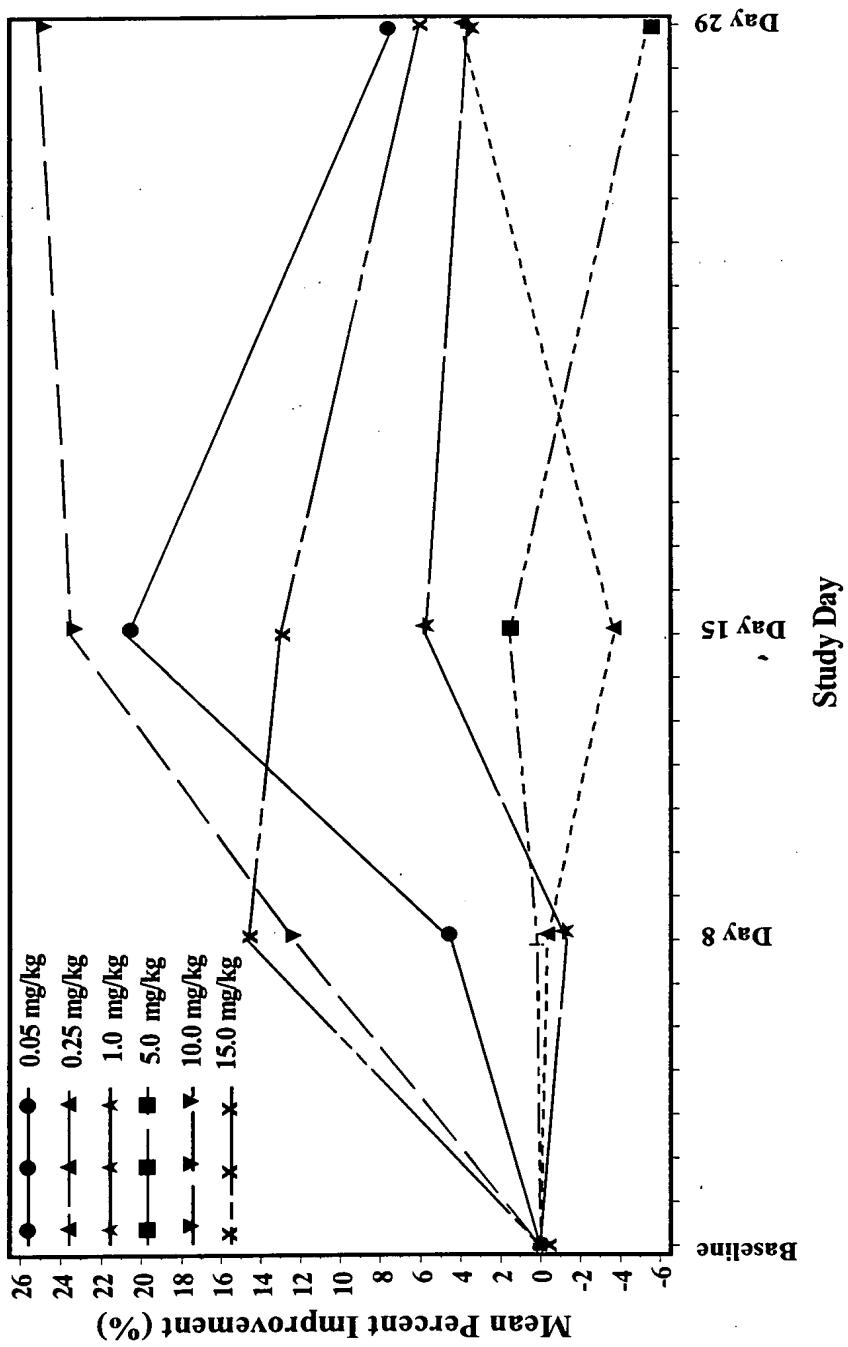


Figure 1. Mean percent improvement in PASI.
 Source: Appendix C.6 (pasi_chg_sumgrf) Physician's Global Psoriatic Assessment Scale

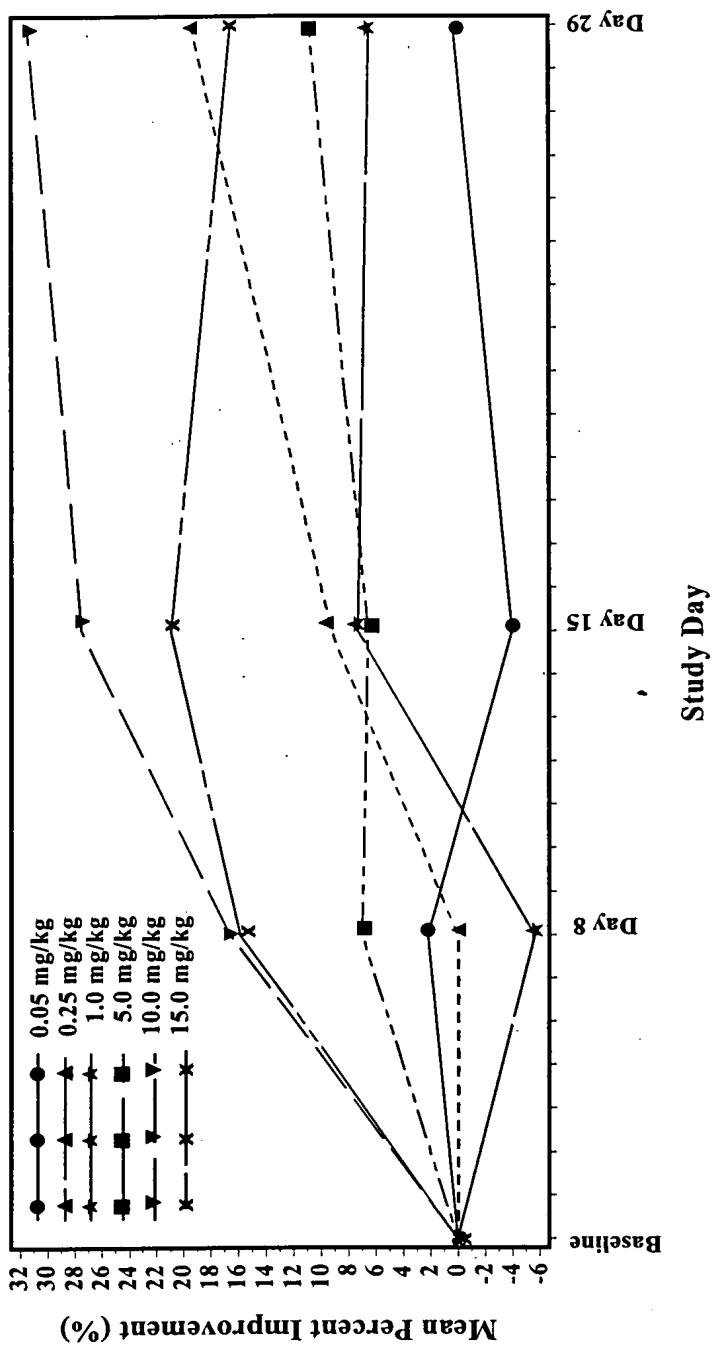


Figure 2. Mean percent improvement in PSS.
Source: Appendix C.5 (pss_dhg_sungrf)

REFERENCES